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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking News
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Editor Peter van de Kerkhof, Radboud University Medical Center, the Netherlands

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Letter from the Editor

Prof. Peter C.M. van de Kerkhof

Dear Reader,

The 28th EADV Congress brought innovations to dermatologists in many respects. In this overview, we have attempted to be balanced and to focus on the presentations which are practically relevant. The new insights into the pathogenesis of inflammatory skin diseases have provided biomarkers that are becoming significant to dermatology. Introduction of new treatments in inflammatory dermatoses requires a critical and adequate positioning of new treatments in daily practice.

In particular in psoriasis, the innovations found their way to real clinical practice: In children with psoriasis anti-IL-17 are currently explored. On ixekizumab, 78% of children with psoriasis reached a PASI 90 response. Comorbidities are also relevant to psoriasis. Studies on the efficacy of treatments in comorbid patients was similar to the efficacy in patients without comorbidities. A remarkable study was presented, showing that patients with moderate-to-severe psoriasis treated with adalimumab had a 58% lower standardised mortality rate compared with the general population. Comorbidities matter and evidence is accumulating that adequate treatment of psoriasis may prevent their development. In atopic dermatitis, treatment innovation is a revolution: various JAK inhibitors, anti-IL-4/IL-13, PDE4 inhibitors, and IL-1 alpha blockade.

Furthermore, this overview provides information on: photo-protection by systemic treatment, comorbidities in urticaria, and a "tracker" to classify rosacea by phenotype, which makes sense as a subdivision in light of treatment selection. The future for inflammatory dermatoses of the skin is bright.

Best regards,
Prof. Peter C.M. van de Kerkhof

Biography

Peter C.M. van de Kerkhof is emeritus Professor of Dermatology and immediate past chairman of the Department of Dermatology of Radboud University Nijmegen. He is currently the coordinating Medical Officer of the International Psoriasis Council and chair of the scientific advisory board of the Dutch burn association. He has been working for many years on the pathogenesis and treatment of psoriasis. He has published more than 700 publications in peer-reviewed journals and has given many presentations on invitation at international conferences. He has served as president of the ESDR, EDF, and the International Psoriasis Council, and was board member of various international societies. Current interests are: pathogenesis and development of biomarkers for psoriasis; real clinical practise research; and personalised medicine.

Conflict of Interest Statement:
Consultancy services for: Celgene, Almirall, Amgen, Pfizer, Philips, AbbVie, Eli Lilly, Galderma, Novartis, Janssen Biotech, Janssen-Cilag, LEO Pharma, Sandoz, Mitsubishi Tanabe, Sandoz, Bristol Meyer Squibb, UCB, Dermavant. Speaker services for: Celgene, Almirall, Eli Lilly, Novartis, Jansen-Cilag, LEO Pharma, Sandoz, Bristol Meyer Squibb.

Late-Breaking News

IL-17A blocker effective in paediatric psoriasis patients

In a phase 3 study, the interleukin (IL)-17 blocker ixekizumab showed a similar efficacy in paediatric patients with moderate-to-severe psoriasis as previously demonstrated in adult patients [1].

Although the first symptoms of psoriasis symptoms present during childhood in one-third of patients, there is still an unmet need for effective and safe therapies for children and adolescents with moderate-to-severe plaque psoriasis. This was the rationale for the IXORA-PEDS study, presented at the EADV Congress by Dr Kim Papp (Probity Medical Research, Canada).

The study evaluated the efficacy and safety of ixekizumab in 203 psoriasis patients between 6 to 18 years old. In a double-blind induction period participants received ixekizumab (n=115; 40 mg, 80 mg, or 160 mg depending on body weight), etanercept (n=30; 0.8 mg/kg), or placebo (n=58) for 12 weeks. At week 12, all participants switched to open-label ixekizumab for the 60-week maintenance phase and the following extension period up to 108 weeks.

The co-primary endpoints of the study were the proportion of patients achieving a ≥ 75% improvement from baseline on their Psoriasis Area and Severity Index score (PASI 75) and a static Physician's Global Assessment (PGA) of clear or almost clear skin (0/1) at week 12. Secondary outcomes included PASI 90, PASI 100, and an improvement of ≥ 4 for patients with an itch Numeric Rating Scale (NRS) score of ≥ 4 at baseline.

At week 12, 89% of patients treated with ixekizumab gained a PASI 75 response compared with 25% in the placebo group and 63% in the etanercept group. In the ixekizumab arm, 81% of patients achieved clear or almost clear skin according the PGA compared with 11% in the placebo group and 40% in etanercept group.

In addition, 78% of patients even achieved a PASI 90 response rate after 12 weeks, compared with 5% in the placebo group and 40% in the etanercept group. A complete clearance of skin lesions (i.e. PASI 100) was achieved by 50% of patients treated with ixekizumab, 20% of placebo-treated patients, and 17% for the etanercept group.

Therapy with the IL-17 inhibitor also led to a reduction in itch: 71% of patients treated with ixekizumab compared to 20% of placebo patients achieved an improvement in itch of ≥ 4 NRS score. As well as a clinically relevant gain in quality of life, assessed in the Children´s Dermatology Life Quality Index: 65% of patients in the ixekizumab group and 23% of placebo patients gained a Children´s Dermatology Life Quality Index result of 0/1 after 12 weeks, which means that quality of life is no longer impaired by psoriasis.

"I think particularly in paediatric patients it is important to look at the safety aspect. We did not see any surprising side effects," said Prof. Papp. Most side effects were mild-to-moderate. One serious event was reported in the double-blind phase, which was not related to ixekizumab but to an overdose of antihistamines. "This study provides encouraging data supporting the potential for ixekizumab to become another treatment option for this patient population," concluded Prof. Papp.

1. Papp KA, et al. Late-breaking abstract D3T01.1B, EADV 2019, 9-13 Oct, Madrid, Spain.

Rituximab beats mycophenolate mofetil in pemphigus vulgaris

Pemphigus vulgaris patients had a 5 times greater likelihood of achieving a complete remission when treated with rituximab compared mycophenolate mofetil (MMF). In addition, the anti-CD20 monoclonal antibody had a superior safety profile.

Prof. Pascal Joly (Rouen University Hospital, France) presented the results of the randomised, clinical, phase 3 PEMPHIX trial, which compared rituximab head-to-head with MMF for the treatment of pemphigus vulgaris [1]. Although MMF is commonly used as a corticosteroid-sparing drug in patients with pemphigus vulgaris, its efficacy has never been proven in a clinical trial. In contrast, rituximab was approved earlier this year by the US authorities and the European Commission for the treatment of adults with moderate-to-severe pemphigus vulgaris. It is the first approved biologic, and therefore a major advancement in the treatment of this rare blistering disease, which can lead to serious, life-threatening fluid loss, infection, and death.

Approval was based on data from the phase 3 Ritux 3 trial, which was also led by Prof. Joly. Ritux 3 demonstrated the superiority of intravenously administered rituximab plus short-term prednisone over high-dose corticosteroid monotherapy [2].

In the more recent phase 3, placebo-controlled PEMPHIX trial, 135 patients with moderate or severe pemphigus were randomised at 49 centres in 10 countries to double-blind rituximab (n=67) or MMF (n=68). The study drug was given on top of background oral prednisone at 1.0-1.5 mg/kg per day, with the steroid to be tapered and discontinued within 4-6 months. Primary endpoint of the study was the proportion of patients at week 52 who had achieved a sustained complete remission lasting for at least 16 weeks while off prednisone. In the rituximab arm, 66 patients completed week 52 compared with 58 patients in the MMF arm.

At week 52, 40.3% of patients in the rituximab arm achieved the primary endpoint compared with 9.5% with MMF (P<0.0001). In addition, rituximab was superior in all secondary efficacy endpoints: patients in the rituximab group had a significantly lower cumulative oral corticosteroid dose: the median cumulative dose was 2,775 mg in the rituximab group compared with 4,005 mg in the MMF group (P=0.0005). The median cumulative dose of corticosteroid was 2.7 g through 52 weeks in the rituximab arm versus 4 g with MMF. A significantly fewer number of flares occurred in patients treated with rituximab compared with MMF (6 vs 44 in the MMF arm; P<0.0001). Five rituximab-treated patients experienced disease flares, in contrast to 26 treated with MMF.

The higher efficacy translated into a significantly greater improvement in health-related quality of life in patients treated with rituximab, assessed with the Dermatology Life Quality Index (DLQI): 61.5% of patients in the rituximab arm had achieved a DLQI score of 0 (i.e. no impairment in health-related quality of life) at week 52 compared with 25% of patients in the MMF arm. Rituximab showed an acceptable tolerability: 9% of the rituximab group and 7.4% of MMF-treated patients had 1 or more treatment related adverse event, a non-significant difference. Serious infusion reactions leading to study withdrawal occurred in 3 patients on rituximab and 1 on MMF. There was a significant difference in favour of rituximab regarding the rate of grade 3 or worse corticosteroid-related adverse events. This was observed in 1.5% of patients with rituximab versus 7.4% with MMF. Overall, rituximab had a superior benefit-risk profile compared with MMF in patients with pemphigus vulgaris. "These results probably mean the end for MMF in pemphigus vulgaris," said Prof. Joly.

1 Joly P, et al. Late-breaking abstract D3T01.1C, EADV 2019, 9-13 Oct, Madrid, Spain.
2 Joly P, et al. Lancet 2017;389:2031-40.

Novel JAK1/2 inhibitor shows remarkable efficacy in alopecia areata

The Janus kinase (JAK) inhibitor CTP-543 showed promising results in patients with moderate-to-severe alopecia areata according to interim results from a phase 2a study [1].

Alopecia areata is a poorly treatable autoimmune disease that affects women, men, and children of all ages. This chronic condition has a remarkable negative impact on quality of life and is associated with anxiety, depression, and other autoimmune conditions.

CTP-543 inhibits both JAK1 and JAK2 and is a modified version of the JAK inhibitor ruxolitinib, currently approved for the treatment of myelofibrosis and polycythemia vera. The double-blind, randomised, placebo-controlled, dose-ranging, phase 2 trial included 149 adult patients with moderate-to-severe alopecia areata. Entry criterion was an at least 50% hair loss as measured by Severity of Alopecia Tool (SALT) score. Patients were randomised to receive 4, 8, or 12 mg CTP-543 or placebo twice daily. Primary efficacy endpoint was a 50% relative reduction in the SALT score from baseline to 24 weeks. Dr James Cassella, chief development officer at Concert Pharmaceuticals (USA), also presented additional clinical endpoints, including the percentage of patients achieving 75% and 90% relative change in SALT at week 24 from baseline and a patient global impression of improvement.

Significantly more patients in the 12 mg and 8 mg group achieved the primary endpoint at week 24 than in the placebo group (47% vs 58%, respectively, compared with 8.6% in the placebo group; both doses P<0.001 vs placebo). The reduction in SALT score in 4 mg group was not statistically significantly compared with placebo. A significant difference compared with placebo was seen after 12 weeks with the 12 mg dosage and after 16 weeks with the 8 mg dosage, but there was still a steep increase of response until week 24. The 12 mg dose was particularly effective: 42% of patients treated with this regimen gained a ≥ 75% change in SALT relative to baseline, 36% a ≥ 90% change in SALT (both comparisons P<0.001 vs

baseline). At week 24, 78% of patients treated with 12 mg and 58% of patients treated with 8 mg rated the disease as "much improved" or "very much approved" (both comparisons P<0.001 vs placebo). "We also saw a very good treatment effect on eyebrow and eyelash growth," said Dr Cassella.

The 12 mg dose was numerically superior and produced a faster onset and greater magnitude of effect compared with 8 mg. Generally, therapy with the novel JAK inhibitor was well tolerated. "There were no real signs of any increase, in particular no differences in grade 3 or 4 haematological changes," said Dr Cassella.

The majority of patients in the 12 mg group continued treatment into a long-term open label extension study. "These promising results support advancement of CTP-543 in the 8 and 12 mg dose into phase 3 trials," concluded Dr Cassella.

1. Cassella J, et al. Late-breaking abstract D3T01.1E, EADV 2019, 9-13 Oct, Madrid, Spain.

Acne highly influenced by climate, pollutants, and unhealthy diet

In an online survey comparing more than 2,800 acne patients to participants without acne, climatic factors, air pollutants, milk products, and sweets as well as a harsh skin routine were identified as exposome factors that affect acne [1].

The exposome comprises all internal and external environmental factors that impact the onset, duration, and severity of a disease. To define the impact of the exposome on acne, an international study was performed in 6 countries (i.e. France, Germany, Italy, Brazil, Canada, and Russia). A total of 10,040 individuals were recruited and data from 6,679 participants was analysed (acne group n=2,826; control group n=3,853). Eligible for inclusion were acne patients who declared that their acne had been diagnosed by a physician or who had benefitted from an acne treatment prescribed by a physician. All participants filled out an online survey designed to evaluate 6 main exposome factors, climate, nutrition, and pollution.

With regard to climatic factors, acne patients lived significantly more often in a particularly hot climate (P<0.001 vs non-acne patients). A significant higher percentage of acne patients had an intense or moderate exposure to the sun in their work or daily activities. "Although sun exposure can improve acne, there are often flares after sun exposure," explained Dr Delphine Kerob (Vichy Laboratories, France) who supported the study.

People with acne were also significantly more exposed to pollutants (i.e. tars, solvent vapours, oil vapours) than those without (P<0.001 for each comparison). Those affected by acne lived significantly more often near the airport or in an area with factories with chimneys (P<0.001 for each comparison).

Western diet aggravates acne vulgaris

Significant differences were also seen with regard to nutrition. Acne patients more often consumed cow´s milk on a daily basis (48% vs 39%, P<0.001), sodas, juices and syrups (35% vs 31%; P<0.001), baked goods, cakes, or pastries (40% vs 28%; P<0.001), chocolate (37% vs 28%; P<0.001), or sweets (23% vs 19%; P<0.001). In addition, they reported more frequently to snack on sugary foods between meals (62% vs 43% ; P<0.001). Whey proteins were consumed more often by acne patients than people without acne (11% vs 7.3%; P<0.001). This is in line with an earlier study that found a close link between acne and a western diet containing refined carbohydrates, milk and dairy products, and saturated fats. This led via multiple pathways to a Th17 activation resulting in inflammation and comedogenesis [2]. Another surprising finding was that 12% of acne patients had used an anabolic steroid or testosterone-based hormonal drug within the previous 12 months, compared with 3.2% of controls without acne.

Skin care routines can also influence acne: the use of facial scrubs, harsh cleansers, and dermarollers was significantly more common among acne patients. "A lot of patients used scrubs that can be responsible for mechanical acne," commented Dr Kerob. Taken together, identifying and reducing the impact of the exposome is important for an adequate disease-management of acne.

1. Kerob B, et al. Late-breaking abstract D3T01.1G, EADV 2019, 9-13 Oct, Madrid, Spain.
2. Melnik MC. Clin Cosmet Investig Dermatol 2015;8:371-88.

JAK inhibition plus TCS lead to high clearance rates in AD

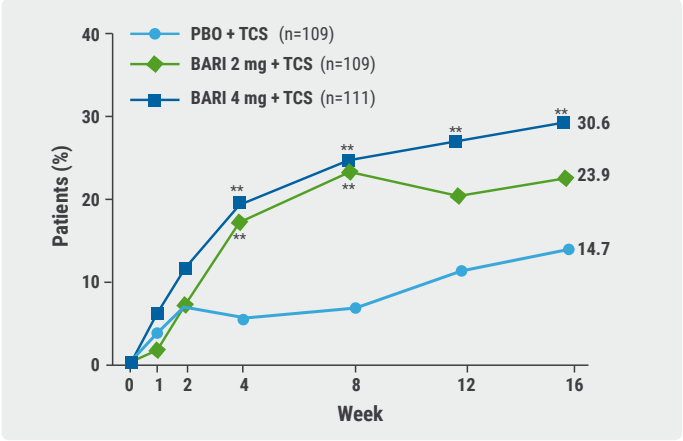
In addition to skin clearance, baricitinib in combination with topical corticosteroid (TCS) showed to be particularly effective in pruritus reduction and improvement of sleep in adult patients with moderate-to-severe atopic dermatitis (AD) [1].

Baricitinib is a selective Janus kinase (JAK) 1 and 2 inhibitor that has previously shown to be effective in moderate-to-severe AD when given as monotherapy. The BREEZE-AD7 study is the first phase 3 study testing the efficacy of a JAK inhibitor in combination with low- and moderate-potency TCS therapy. "I think the BREEZE-AD7 study is important because it allows to look more into the real world where we use a systemic drug together with TCS," said Prof. Kristian Reich (University Medical Center Hamburg-Eppendorf, Germany).

The study included 329 adult patients with moderate-to-severe AD for ≥ 1 year. Participants were treated in 3 arms: either placebo and TCS, or baricitinib in a dose of 2 or 4 mg and TCS. Primary study endpoint was the Investigator´s Global Assessment (IGA) of clear or almost clear (0/1) with an at least 2-point improvement from baseline. Secondary endpoints included a change in Eczema Area and Severity Index (EASI), itch improvement in Numeric Rating Scale (NRS) score, and improved sleep disturbances.

Baricitinib plus TCS showed an early onset of response, but only the 4 mg dose was significantly more effective after 16 weeks: 30.6% of patient reached the primary endpoint compared with 14.7 in the placebo plus TCS group (P≤0.01; see Figure). At week 16, nearly half of the patients (47.7%) taking the higher dose reached an EASI 75 response.

Figure: 4 mg Baricitinib resulted in a significantly higher percentage of patients that achieved an at least 2-point improvement from baseline of IGA 0/1 compared to placebo + TCS (primary endpoint) [1]



BARI, baricitinib; IGA, Investigator Global Assessment; PBO, placebo; TCS, topical corticosteroids. P≤0.01 versus placebo (unadjusted analysis).

"We have underestimated the importance of itch and pain in AD and their effect on sleep," said Prof. Reich. Significant improvement in itch was detected as early as week 2 for 4 mg and week 3 for 2mg. After 16 weeks, itch was reduced by 43.4% in patients treated with 4 mg baricitinib and TCS. Therapy also led to a quick improvement of sleeplessness: after 16 weeks, more than 60% of nights were not disrupted in the high-dose group.

The combination of baricitinib and TCS also led to a fast improvement of skin pain: after 16 weeks, nearly 50% of patients reached a skin pain improvement in a NRS of ≥ 4 points. Not surprisingly, these results translated into a dramatic impact on quality of life: at 16 weeks, 23.4% of patients treated with the high dose reached a DLQI 0/1 response, which means that quality of life is no longer impaired by the disease.

A post-hoc analysis showed a dose-dependent increase of TCS-free days from baseline to week 16: 32.9% TCS-free days were gained in the high-dose group. In 16 days, 137 g less TCS was used in this group.

"In 16 weeks, we saw no difference in serious adverse events between the groups. Of course, we have to see longer term data to judge the safety," said Prof. Reich. Acne was observed, which has to be monitored in the future. One pulmonary embolism was reported in the high-dose group. In conclusion, baricitinib may be another promising novel oral treatment option for patients with moderate-to-severe AD, which seems to be strongest in itch and sleep disturbance reduction.

1 Reich K, et al. Late-breaking abstract D3T01.1H, EADV 2019, 9-13 Oct, Madrid, Spain.

No cancer risk with long-term use of tacrolimus, a topical calcineurin inhibitor, in children with AD

Children that regularly use the topical calcineurin inhibitor tacrolimus over more than 10 years face no elevated risk of cancer. This was the result of an observational study including more than 44,000 patient-years of follow-up [1].

"Atopic dermatitis is a chronic disease requiring long-term treatment. Therefore, we need prospective safety studies to evaluate the cancer risk," said Prof. Regina Fölster-Holst (University Medical Center Schleswig-Holstein, Germany). A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis (APPLES™) is an international observational study designed to address the possibility of increased lymphoma or other cancer risk in patients treated long-term with topical calcineurin inhibitors.
The primary outcome was occurrence of any malignancy. In addition, incidences of lymphoma or cutaneous malignant

melanoma were assessed. Standardised incidence ratios for cancer events were compared to sex-, age-, and race-matched background population data from national cancer registries.

Between May 2005 and August 2012, APPLES enrolled 7,954 eligible patients at 314 sites in 9 North American and European countries. Participants were children with atopic dermatitis (AD) with exposure to topical tacrolimus for at least 6 weeks and who were first exposed before the age of 16. Most patients suffered from modest-to-severe AD, and the majority also had other atopic diseases. Patients were observed over 10 years under actual-use conditions, with regular clinic visits and completion of questionnaires by the patients or their parents or caregivers. Median study persistence was 6.4 years, with 14.7% of patients remaining on-study for ≥ 10 years. In 2019, the FDA endorsed an early stop in 2019 due to futility of continuation as they thought it unlikely that continued observations could alter the study findings.

During the study, 6 cases of cancer occurred but no lymphoma. No difference was observed in cancer incidence to the matched background population data. "Even if we increase the hypothetical incidence to 2.5, the cancer incidence would remain non-significantly elevated over the expected background population rate," said Prof. Fölster-Holt.

With regard to the safety of the product, it is very reassuring that there has been no incidence of lymphomas and only one case of skin cancer was observed over more than 44,000 patient-years of follow-up. As the evaluation only included data on tacrolimus, the results cannot be transferred to other calcineurin inhibitors like pimecrolimus.

1 Fölster-Holst R, et al. Late-breaking abstract D3T01.1J, EADV 2019, 9-13 Oct, Madrid, Spain.

Green light for a second JAK inhibitor in AD

Monotherapy with the Janus kinase (JAK) inhibitor abrocitinib demonstrated remarkable efficacy: significant differences in skin clearance compared with placebo could be shown as early as 2 weeks in the phase 3 JADE MONO-1 trial [1].

After positive results in phase 2 trials [2], the 100 mg and 200 mg doses of abrocitinib were assessed in a phase 3 trial. Adolescents (> 12 years) and adults with moderate-to-severe atopic dermatitis (AD) were included and treated with the 2 dosages or placebo. The co-primary endpoints in JADE MONO-1 were achievement of an Investigator Global Assessment (IGA) score of 0 or 1 at week 12 and an EASI 75 response. "With a mean EASI score of about 30 at baseline, we treated a population quite impacted by the disease," said Prof. Eric Simpson (Oregon Health & Science University, USA).

A clear-cut dose response was evident in the trial: the IGA response rates were 43.8% in the 200 mg dose group, 23.7% with 100 mg, and 7.9% with placebo. The EASI 75 response rates were 62.7%, 39.7%, and 11.8%, respectively, with a statistically significant separation from placebo already by week 2. Abrocitinib leads to a significant itch reduction: 57.2% in the high-dose group and 37.7% of patients in the low-dose group achieved an at least a 4-point improvement in itch on the Numeric Rating Scale (NRS) compared with 15.3% in the placebo group.

Abrocitinib showed an acceptable short-term safety profile. There were no cases of malignancy or major cardiovascular events. Laboratory evaluations revealed that there is a decrease in platelet count but without clinical sequelae. In addition, a dose-related ~10% increase in LDL-cholestrol and 20% decrease in HDL-cholesterol were observed.

1 Simpson E. Late-breaking abstract D3T01.1I, EADV 2019, 9-13 Oct, Madrid, Spain.
2 Gooderham MJ, et al. JAMA Dermatol 2019 Oct 2 [epub ahead of print].

Topical ruxolitinib effective in vitiligo

Vitiligo pathogenesis is driven by signalling through Janus kinase (JAK) 1 and 2. In a clinical trial, topical ruxolitinib cream produced substantial facial and total body repigmentation up to 1 year [1].

Vitiligo is a chronic autoimmune disease of the skin that targets melanocytes, resulting in patches of skin depigmentation [2]. Expression of interferon (IFN)-γ is increased in the lesional skin of patients. Neutralisation of IFN-γ prevents CD8(+) T-cell accumulation and depigmentation, suggesting a therapeutic potential for this approach [3]. Thus, JAK1/JAK2 inhibitors appear effective in vitiligo, presumably via inhibition of IFN-γ signalling in the skin [4].

Ruxolitinib cream across a dose range of 0.15 to 1.5% provided significant repigmentation of facial vitiligo lesion after 24 weeks of double-blind, vehicle-controlled treatment [5]. After the blinded study phase, all patients were re-randomised and then treated with 1.5% ruxolitinib cream for 52 weeks. Primary endpoint was the proportion of patients who achieved a ≥ 50% improvement in the Vitiligo Area Scoring Index (VASI) in the face at week 24 compared with patients treated with vehicle. The proportion of patients achieving ≥ 50% improvement in

facial VASI at week 52 was a secondary endpoint. Participants (n=157) had depigmentated areas of ≥ 0.5% of total body surface area (BSA) on the face and ≥ 3% on non-facial areas. Most of the participants were middle aged (mean age 48 years) and 84% of them were Caucasian.

At week 24, a ≥ 50% improvement in the facial VASI (primary endpoint) was achieved by a significantly greater proportion of patients receiving ruxolitinib cream versus vehicle. Continued improvement was seen through 52 weeks of treatment. At week 52, the proportion of patients achieving this response was highest in the 1.5% ruxolitinib group: 57.6% of patients reached this endpoint. At week 52, more than half of the patients (51.5%) even achieved an improvement in VASI of the face by 75%, and a third of patients by 90%. In addition, the total VASI improvement by 50% was noticed in a dose-dependant manner. Ruxolitinib cream was not associated with clinically significant application site reactions or serious treatment-related adverse events.

"I have waited 30 years for a study in vitiligo with these results," said Prof. Amit Pandya (University of Texas Southwestern Medical Center, USA) during the presentation of the results.

1 Pandya A. Late-breaking abstract D3T01.1L, EADV 2019, 9-13 Oct, Madrid, Spain.
2 Taieb A, Picardo M. N Engl J Med 2009;360:160-9.
3 Harris JE. J Invest Dermatol 2012;132:1869-76.
4 Liu LY, et al. J Am Acad Dermatol 2017;77:675-82.
5 Rosmarin D, et al. Poster presented at WCD 2019, 10-15 June, Milan, Italy.

Emerging Therapies

Small molecules: interesting novel treatment options in AD

There is a high need for oral treatments for atopic dermatitis (AD) that cannot be controlled with local therapy. Both phosphodiesterase (PDE) inhibitors and Janus kinase (JAK) inhibitors are interesting approaches [1].

PDE4 is involved in the regulation of pro-inflammatory cytokines via the degradation of cyclic adenosine monophosphate. Targeting PDE4 reduces the production of pro-inflammatory mediators in AD and may be an interesting treatment target with a favourable safety profile [2]. Apremilast, an orally available PDE4 inhibitor, is approved for the treatment of adults with moderate-to-severe psoriasis and active psoriatic arthritis. This immune modulator regulates a number of the pro-inflammatory signals involved in AD, including IL-17, IL-22, IL-13, and IL-31 [3].

A phase 2 study published earlier this year evaluated the treatment effect of 30 mg and 40 mg of apremilast on skin clearance, assessed in EASI percentage change from baseline in patients with moderate-to-severe AD [4]. After 12 weeks, the 40 mg dose led to a modest but statistically significant improvement of -31.6% compared with -11% in the placebo group (P<0.04). A biopsy substudy showed that apremilast reduced the mRNA expression of inflammatory markers associated with the Th17/Th22 pathways. More adverse events were observed within the 40 mg group. Due to 6 cases of cellulitis, an independent safety monitoring committee discontinued the study. "These results are disappointing; however, AD is a heterogeneous disease and we have to stratify patients that may have a benefit," said Prof. Tilo Biedermann (Helmholtz Center Munich, Germany).

A topical PDE4 inhibitor that has been FDA approved for AD is crisaborole ointment. Evidence from phase 3 trials demonstrating that crisaborole is an efficacious topical agent for mild-to-moderate AD with a favourable safety profile and limited systemic exposure [5].

JAK inhibitors enter the therapeutic arena

"The JAK inhibitors are really the most important novel oral drug class in AD," said Prof. Biedermann. There are several differences between the JAK inhibitors depending on the cytokine pathway they influence [6]. An in vitro study showed that the different JAK inhibitors modulate distinct cytokine pathways to varying degrees. JAK inhibitors can be used topically and systemically. Tofacitinib ointment was shown to be effective in patients with mild-to-moderate AD [7]. Patients treated with the tofacitinib ointment showed significant improvements versus vehicle across all efficacy endpoints and for pruritus [7]. "However, the main theme is systemic treatment with JAK inhibitors," said Prof. Biedermann. A phase 2 study published this year showed that 61% of

patients treated with oral baricitinib plus TCS achieved an EASI 50 response compared to 37% with placebo plus TCS. Baricitinib also improved pruritus and sleep loss [8]. "Their efficacy may not reach dupilumab but it is not bad," said Prof. Biedermann. "With the new drugs we understand that TH2 cytokines are really in the centre of AD pathogenesis; this is even more important," concluded Prof. Biedermann.

1 Biedermann T. D1T01.1B, EADV 2019, 9-13 Oct, Madrid, Spain.
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IL-1α blockade: a new treatment option in AD

IL-1α blockade is a novel interesting target in atopic dermatitis (AD). In a proof-of-concept study, an IL-1 blocker improved AD in all disease measures [1].

"The rationale behind targeting IL-1α is that Th1 immunity plays a signifying role in adults with chronic AD," said Prof. Alice Gottlieb (Icahn School of Medicine at Mount Sinai, USA). Under the influence of a variety of cytokines, including IL-17A and IL-17C, keratinocytes increase release of IL-1α. This cytokine drives leukocyte recruitment and activates the vascular endothelium [2]. By potentiation of nociceptors, itch is increased. It stimulates expression of matrix metalloproteinases, thus impairing the skin barrier [3]. This results in skin inflammation, epidermal barrier defects, and severe, debilitating itch, and these factor are all hallmarks of AD [4,5]. IL-1α on circulating leukocytes may also drive inflammatory signalling in the microvasculature of lesions. In addition, it induces breakdown of the skin barrier by prompting matrix metalloproteinases. In animal studies, IL-1α has shown to induce pruritus [6].

Therefore, an open-label, proof-of-concept, multicentre study evaluated the safety and efficacy of bermekimab, a monoclonal antibody targeting IL-1α, in patients with moderate-to-severe AD [1]. Participants were treated with 200 mg bermekimab (n=10) or 400 mg bermekimab (n=28). Injections were given weekly for 4 or 8 weeks, respectively.

After 8 weeks, patients treated with 400 mg bermekimab achieved an improvement in the EASI by 75% from baseline, and a reduction in the Scoring of Atopic Dermatitis (SCORAD) by 67% (both differences P<0.0001). In addition, patients gained a significant better quality of life: 61% of patients in the high-dose group ended with a Dermatology Life Quality Index score of 0/1, which means that the disease no longer has an impact on their quality of life. Overall, 80% of patients treated with the higher dose achieved an improvement in pruritus (worst and average itch) scores on a Numeric Rating Scale of ≥ 4 points (see Figure). Significant improvements were also seen in anxiety and depression. At the beginning of the study, 71% of patients said they had a pain score of 7 out of 10. After 8 weeks, this was improved by more than 80%.

There were 25 non-serious adverse events, which included no major adverse cardiac events and no neoplasms. Injection-site reactions were reported by 3%. The 400 mg dose provided greater efficacy without an increase in side effects. "The only side effects we noticed were grade 1 injection site reactions and nausea in 3 subjects. This surely is early data but it is still a nice study," concluded Prof. Gottlieb.

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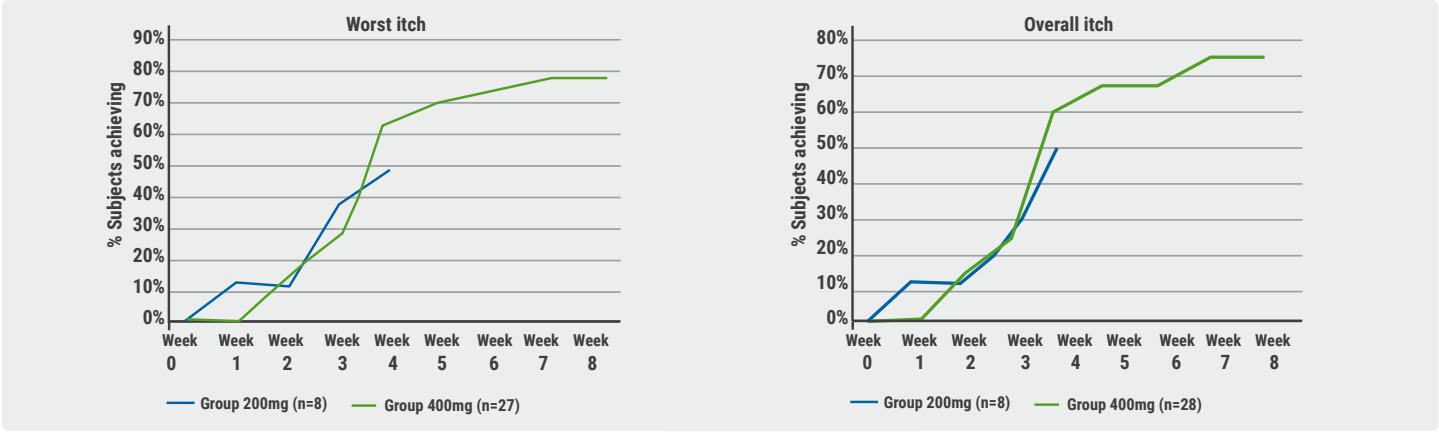
Figure: 80% of patients achieved a ≥4 points reduction in the worst and average itch NRS score [1]



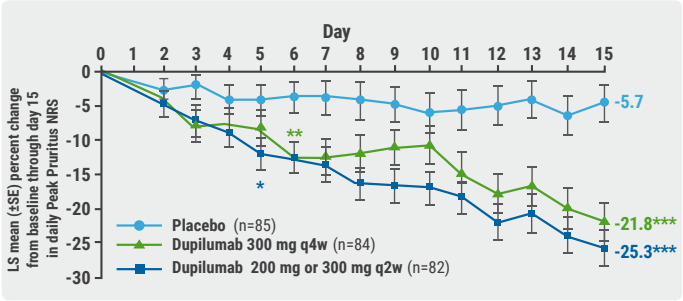
IL-4/IL-13 blockade leads to rapid itch reduction in adolescents

A post-hoc analysis of the phase 3 trial LIBERTY AD ADOL showed that dupilumab entails a rapid itch reduction after only 5 days in adolescents with moderate-to-severe atopic dermatitis (AD) [1].

Itch is the moth bothersome symptom for patients with AD most and it is furthermore associated with sleep loss, reduced quality of life, and reduced productivity. "With our analysis, we wanted to find out how long it will take to relieve itch. This is especially interesting in comparison with JAK inhibitors," said Prof. Eric Simpson (Oregon Health & Science University, USA). The LIBERTY AD ADOL trial included 251 adolescent patients (aged 12 to 18 years). They were randomised to subcutaneous dupilumab every 2 weeks in 2 dosages according to body weight (< 60 kg or ≥ 60 kg), dupilumab every 4 weeks, or placebo over 16 weeks. The co-primary endpoints of the study were: percentage of participants with almost clear or clear skin according to the Investigator Global Assessment (IGA) score (0/1 score) and reduction from baseline of ≥ 2 points, and percentage of patients with an improvement of the EASI score by 75%. These endpoints were met in all dupilumab treated patients.

The current analysis evaluated change from baseline through day 15 in daily Peak Pruritus Numerical Rating Scale (NRS) scores (see Figure). The Peak Pruritus NRS is a well-defined, reliable, sensitive and valid scale for evaluating worst itch intensity in patients with moderate-to-severe AD [2]. It measures the intensity of worst itch in the previous 24 hours on a scale of 0-10.

Figure: Change from baseline (%) through day 15 in daily Peak Pruritus NRS scores [1]



*P<0.05; **P<0.01; ***P<0.0001 vs placebo.
LS, least squares; SE, standard error; q2w, every two weeks; q4w, every four weeks.

Treatment with dupilumab resulted in rapid and significant improvement of itch in adolescent patients with moderate-to-severe AD as early as day 5 in those patients treated with dupilumab every 2 weeks or day 6 in patients treated with dupilumab every 4 weeks. A clinically meaningful improvement was already observed from day 13 in those receiving dupilumab every 2 weeks.

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How to manage conjunctivitis in AD patients treated with a biologic

The IL-4/IL-13 blocker dupilumab is the first approved biologic for therapy with atopic dermatitis (AD). It is remarkably effective, but a relatively frequent side effect is conjunctivitis, which is best managed preventively [1].

Dupilumab is a highly effective therapy for patients with moderate-to-severe AD. When applied together with topical corticosteroids, 39% of patients gained a complete or almost complete healing of skin lesions (corresponding to IGS 0/1) with this drug, which could be maintained over a year [2]. "This is a huge step forward for the management of patients with moderate-to-severe disease," said Prof. Tilo Biedermann (Helmholtz Center Munich, Germany). In real life, he has seen a very similar effect: patients respond quickly and about half of patients gain an EASI 90 response after 8 weeks.
"A small drawback of this effect is the conjunctivitis, which we see in 8 to 10% of our patients," said Prof. Biedermann. Pathogenesis, clinical characteristics, and treatment options for this conjunctivitis are still not characterised well. Typical symptoms are redness in both eyes and tearing. Further symptoms such as itch, stinging, burning, and foreign body sensation are seen in most but not in all patients [3].

Prof. Biedermann pointed out that this side effect could best be managed by preventive treatment with an emollient for the eyelids. Another possibility is the use of topical pimecrolimus cream. In addition, artificial tears should be used both in advance and after conjunctivitis has occurred. "In most cases we encounter mild forms of conjunctivitis that can be managed with eye drops containing hyaluronic acid or without treatment," said Prof. Biedermann. In his experience, antihistamines are not effective in dupilumab-related conjunctivitis. The incidence of conjunctivitis was associated with both AD severity and prior history of conjunctivitis [4]. In severe cases, eye drops containing fluorometholon (0.1%) or ciclosporine (1mg/ml eye drops) proved to be effective [3].

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Biologics: increasingly used in paediatric dermatology

Biologics and cytokine blockers are increasingly used in children and adolescents with moderate-to-severe psoriasis and atopic dermatitis (AD). Data shows that they cause less side effects than systemic conventional therapies [1].

In adults, biologics targeting specific cytokines are effective, well tolerated, and a safe alternative to conventional systemic treatments. At present, 3 biologics (i.e. etanercept, adalimumab, and ustekinumab) are approved in paediatric psoriasis and dupilumab is approved in AD.

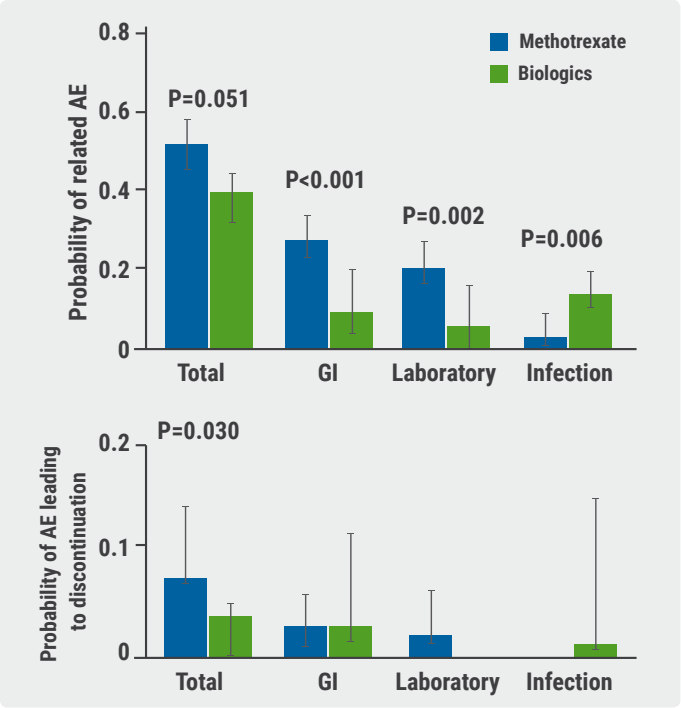
TNF-blockers and ustekinumab showed similar efficacy and tolerability compared with trials in an adult population [2-4]. In the meantime, long-term data from open-label extensions with TNF-blockers showed reassuring results. After 5 years, etanercept was still well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks [5]. There were no opportunistic infections or malignancies. Similarly, 52-week data from adalimumab showed no malignancies but nasopharyngitis and headache was reported in > 20% of patients and injection-site reactions in 3.7% [6,7]. One study included not only patients with psoriasis but also with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, and Crohn's disease. The safety profile was generally similar across indications [7].

Real-world data confirms safety in paediatric psoriasis

Real-world studies can provide further insight into the true benefit of a therapy beyond randomised controlled trials with their strict inclusion criteria. A retrospective review was conducted on the use of systemic treatments for moderate-to-severe psoriasis in children in 20 centres in the USA and Europe. All children with moderate-to-severe psoriasis who used systemic medication or phototherapy for at least 3 months were included [8]. Mean duration of treatment was 20 months with biologics and 18.7 months with methotrexate. In this review, 270 children were treated with methotrexate and 106 with biologics (primarily etanercept). Medication-related adverse events occurred less often with biologics than with methotrexate. There were less gastrointestinal side effects, less laboratory issues, and less adverse events leading to treatment discontinuation, but more infections with biologic therapy (see Figure) [8].

A second real-life study was performed in France, including 134 children with moderate-to-severe psoriasis in 30 centres [9]. The

Figure: Paediatric patients treated with biologics have less gastrointestinal side effects, lab issues, adverse events leading to treatment discontinuation than methotrexate. Yet, more infections occurred with biologics [8]



AE, adverse events; GI, gastrointestinal.

mean age of onset of treatment was 7.2 years and the mean age at onset of treatment with a biologic 13.2 years. Altogether, the study observed 232 years of cumulative treatment. During this period, 7 serious adverse events were documented: 3 serious infections, 2 cases of weight gain, 1 psoriasis flare, and 1 malaise [9]. Ustekinumab had the best drug survival outcome in this study. Similarly, dupilumab was equally effective and had a similar safety profile in paediatric patients with moderate-to-severe AD compared with adult patients [10]. "Basically dupilumab has the same side effects in children as in adults, including conjunctivitis," said Prof. Marieke Seyger (Radboud University Nijmegen, the Netherlands).

Biologics are effective in both psoriasis and AD and show reassuring safety profiles. Further research and post-marketing registries are needed to collect long-term safety data of this particular sensitive patient population. "Taken together, biologics are generally associated with less treatment-related toxicity than conventional systemic agents," concluded Prof. Seyger.

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Spotlight on Psoriasis

IL-17 blocker: effective and safe in patients with comorbidities

An analysis of psoriasis patients with comorbidities included in four phase 3 trials showed that secukinumab exhibits a comparable efficacy and safety in patients with comorbidities at baseline [1].

Today, psoriasis is seen as a chronic inflammatory systemic disease. Research has shown that different comorbidities commonly found in patients with psoriasis, such as arthritis, depression, inflammatory bowel disease, and cardiovascular diseases, are directly related to the chronic inflammatory status of psoriasis, and may thus influence efficacy and safety of drug treatment [2].

The IL-17 blocker secukinumab has demonstrated long-lasting efficacy and safety in the complete spectrum of manifestations of psoriatic disease. An analysis of pooled data from four phase 3 trials (i.e. ERASURE, FIXTURE, FEATURE, and JUNCTURE) assessed the incremental burden of comorbidities on clinical efficacy and safety among patients with moderate-to-severe psoriasis.

A total of 880 patients with baseline comorbidities were included in the analysis. Patients suffered from cardiovascular diseases (i.e. hypertension, angina, myocardial infarction, congestive heart failure, coronary artery disease, and cardiac arrhythmias), metabolic diseases (i.e. obesity, hyperlipidaemia, and diabetes), and musculoskeletal diseases (i.e. osteoarthritis, rheumatoid arthritis, and psoriatic arthritis), and psychiatric disease (i.e. depression).

At week 12, patients treated with secukinumab (150 mg or 300 mg) were more likely to achieve Psoriasis Area and Severity Index (PASI) 75, PASI 90, and clear or almost clear skin according to the IGA (0/1 Score) compared with those receiving placebo or etanercept (see Figure; P<0.05 for all comparisons). More patients treated with secukinumab than with placebo achieved PASI 100 and IGA 0 responses. Reassuringly, despite their comorbidities, patients did not suffer more frequently from treatment emergent adverse events, serious adverse events, and treatment emergent adverse events leading to study discontinuation compared with patients without comorbidities. No new safety signals were identified.

This post-hoc analysis showed that treatment with secukinumab significantly improved clinical outcomes and was well tolerated in a cohort of patients with moderate-to-severe psoriasis and active baseline comorbid conditions.

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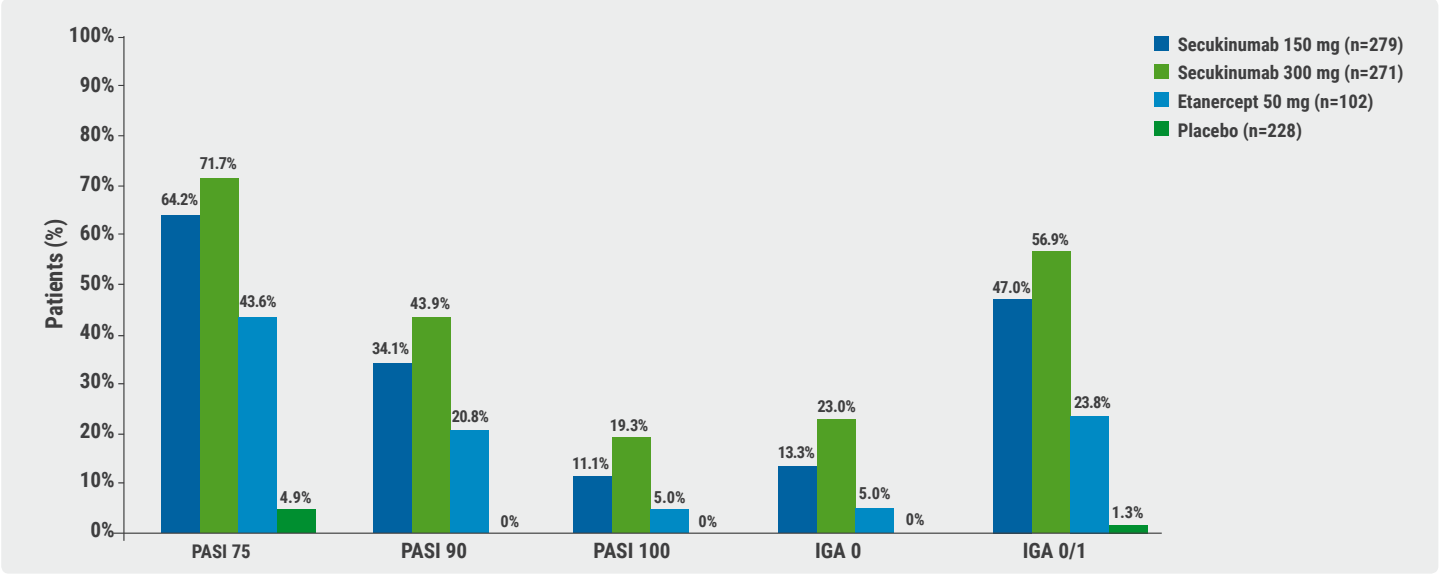
Figure: Week 12 efficacy outcomes among patients with psoriasis and baseline comorbidities [1]



ESPRIT registry: sharp decline in mortality in patients treated with a TNF blocker

An analysis of registry data showed that patients with moderate-to-severe psoriasis treated with adalimumab had a 58% lower standardised mortality rate compared with the general population [1].

ESPRIT is an ongoing international, prospective, observational registry evaluating the long-term safety and effectiveness of the TNF blocker adalimumab in adults with moderate-to-severe chronic plaque psoriasis under real-world conditions. Ten-year data was analysed from 6,014 psoriasis patients with collectively 28,161 person-years on adalimumab in routine clinical practice.

"You may not believe it if someone tells you that you, as a dermatologist, can save patient lives by controlling psoriasis," said Prof. Diamant Thaçi (University of Lübeck, Germany). Yet, this was exactly what the data showed: the standardised mortality ratio in participants in the ESPRIT registry was 58% lower than expected. A total of 144 deaths were predicted in the matched general population, yet only 60 deaths occurred in adalimumab-treated registry participants.

In addition, the incidence rates of serious infections, malignancies, and cardiovascular events in ESPRIT participants remained stable over time and well within the range of published rates in psoriasis patients not on biologic therapy. No new safety signals were observed and safety was consistent with the known safety profile of adalimumab.

As Prof. Thaçi pointed out, the positive mortality result is unexpected because the ESPRIT participants were typical for patients with moderate-to-severe psoriasis one usually encounters in clinical practice: many of them have cardiovascular risk factors, e.g. obesity and a substantial burden of comorbid conditions. The efficacy of adalimumab remained stable over the 10-year- period. "This result demonstrates the importance of good control of psoriasis," concluded Prof. Thaçi.

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Relationship psoriasis and NAFLD: new data on the hepato-dermal axis

A Spanish study showed for the first time that more severe hepatic damage is evident in patients with both psoriasis and non-alcoholic fatty liver disease (NAFLD) [1].

Over the past 10 years, it has become increasingly evident that NAFLD is a multisystemic disease that affects extra-hepatic organ systems and interacts with the regulation of several metabolic and immunological pathways [2]. The prevalence of NAFLD (diagnosed by imaging or by histology) is remarkably higher in psoriatic patients, occurring in up to 50% of patients [2]. Of note, this association is evident even after adjusting for metabolic syndrome traits or other potential confounders. Up to now, no reports on a possible link between the severity of both conditions have been published.

To explore a possible association, a total of 64 male patients were included in a prospective 12-month study. Inclusion criteria were NAFLD (histologic steatosis >5%, sonographic steatosis >48 dB/m, no other hepatic conditions, and less than 30 g/d of alcohol intake) and severe psoriasis. Patients enrolled in the trial had a considerable comorbidity: their mean body mass index was 30.9 kg/m2, 53.1% had diabetes mellitus, and 42.2% suffered from hypertension. The Psoriasis Area and Severity Index score was used to measure the severity of psoriasis, while ultrasound elastography was used to judge the severity of NAFLD.

Results showed that psoriatic patients with NAFLD had indeed more severe elastographic hepatic damage if they had a higher level of psoriasis severity. "In this context, increasing awareness and the continued assessment of the severity of NAFLD in patients with psoriasis by primary care physicians, specialists, health policy makers, and patients should be prioritised to help manage both conditions," said lead researcher Dr Daniel Nieto (La Paz Hospital, Spain).

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Novel selective IL-23 blocker equally effective in patients with metabolic syndrome

Two post-hoc analyses of data from the reSURFACE 1 and 2 studies compared the efficacy of tildrakizumab in people with and without metabolic syndrome. Surprisingly, no difference was observed in efficacy between these groups [1,2].

Obesity and metabolic syndrome are common comorbidities in patients with moderate-to-severe psoriasis. The adipose tissue is a complex organ that secretes several adipokines, involved in the regulation of several metabolic processes. The unbalanced production of pro- and anti-inflammatory

adipokines in obesity contributes to the development of a chronic low-grade inflammation state, which seems to favour worsening of psoriasis lesions and a poorer response to treatment [3]. Previous data has shown that obese patients often show a reduced response to therapy [4]. The metabolic syndrome can also have a negative impact on long-term drug survival of biologic treatment [5].

Tildrakizumab is a selective IL-23 blocker for therapy of chronic plaque psoriasis. Its efficacy and safety was assessed in the phase 3 trials reSURFACE 1 and reSURFACE 2. In a post-hoc analysis, efficacy was analysed in patients who had metabolic syndrome at baseline compared with patients without this comorbidity in both studies [1,2].

At 3 years, the proportion of patients who achieved PASI 75/90/100 was comparable between those with and without metabolic syndrome in both studies. In the reSURFACE 1 study, 69% of patients with metabolic syndrome compared with 71% without this comorbidity achieved a PASI 75 response [2]. The corresponding percentages for PASI 90 response were 42% versus 51% of patients without metabolic syndrome.

In addition, 3-year adverse event rates usually associated with metabolic syndrome were comparable in study participants with and without metabolic syndrome. These results show that tildrakizumab can help patients with moderate-to-severe plaque psoriasis, regardless of the presence of a metabolic syndrome achieve and maintain significant long-term skin clearance over.

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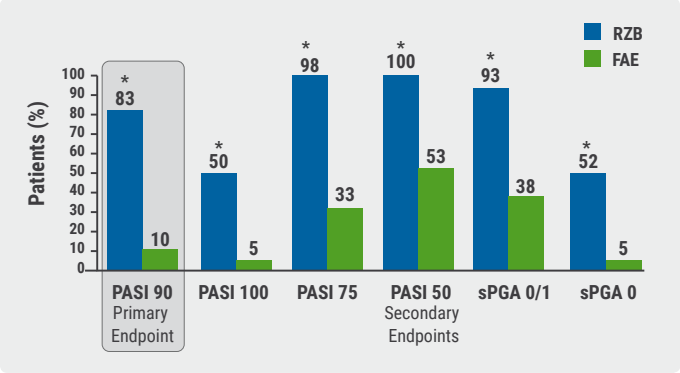
Selective IL-23 blocker crushes fumaric acids in all assessed efficacy endpoints

A head-to-head comparison of the selective IL-23 blocker risankizumab with oral fumaric acid esters in treatment-naïve patients with moderate-to-severe psoriasis demonstrated superiority of the biologic in all assessed efficacy endpoints at week 24 [1].

In the Netherlands, Germany, the United Kingdom, and Ireland, fumaric acid esters are frequently used for systemic therapy of moderate-to-severe psoriasis [2-4]. A new head-to-head trial included systemic treatment-naïve adult patients with chronic moderate-to-severe plaque psoriasis of at least 6 months duration. All patients qualified for systemic therapy: they had a psoriasis area and severity index score >10, an affected body surface area of >10%, and their quality of life was severely impaired (dermatology life quality index score of >10). Patients were randomised to receive subcutaneous risankizumab 150 mg at weeks 0, 4, and 16 (n=60) or oral fumaric acid esters in increasing doses from week 0 to week 24 (n=57).

At the end of the study, 83% of patients receiving risankizumab achieved the primary endpoint of PASI improvement by 90% compared with only 10% of patients in the fumaric acid ester arm (see Figure). This striking superiority was also demonstrated in the static physician's global assessment (sPGA). Starting at week 4, significantly more patients in the risankizumab arm achieved clear or almost clear skin lesions (corresponding to sPGA 0/1) than patients treated with fumaric acid esters.

Figure: Summary of efficacy results at week 24 [1]



*P<0.001 vs fumaric acid esters
FAE, fumaric acid esters oral formulation; PASI, Psoriasis Area and Severity Index; RZB, risankizumab; sPGA, static Physician's Global Assessment.

At the end of the study, over 90% of patients treated with the cytokine blocker achieved the endpoint compared with less than half of patients treated with fumaric acid esters. "Significantly more patients randomised to risankizumab achieved clear or almost clear skin earlier than patients randomised to fumaric acid esters," said Prof. Diamant Thaçi (University of Lübeck, Germany). This superiority was mirrored in a high percentage of patients achieving a quality of life that was no longer impaired by the psoriasis: 67% of patients treated with the biologic compared with 10% of patients in the fumaric acid group reached this endpoint.
Adverse events were similar between groups, with 82% of patients in the risankizumab arm experiencing any adverse event compared with 100% of patients in the fumaric acid ester arm.

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No hint of teratogenicity through ixekizumab

An analysis of participants from 16 clinical trials who were accidentally exposed to ixekizumab during pregnancy showed no signs of congenital malformations outcomes [1].

In an analysis, presented by Prof. Alexander Egeberg (Herlev and Gentofte Hospital, Denmark), pregnancy outcomes of patients exposed to the interleukin 17 blocker ixekizumab in clinical trials were assessed and compared with respective US National Vital Statistic System (NVSS; 2017) birth records and data from the multicentre longitudinal, observational registry PSOLAR (Psoriasis Longitudinal Assessment and Registry; June 2007 to August 2012). In total, 2,499 female and 4,517 male patients fathering a pregnancy were exposed to ixekizumab in 16 clinical trials. Data on live births, spontaneous and induced abortions, and congenital malformations were provided for maternal and paternal exposures.

Most female patients were exposed to ixekizumab during the first trimester (n=46; 92%). Out of 50 female patients (2%) who were exposed during the pregnancy, 44 had a known outcome. These pregnancies lead to 24 live births (54.5%); 75% of them were full term, 16.7% premature. There were 9 spontaneous abortions (20.5%) and 11 induced abortions (25%). No congenital malformations were reported for women exposed to ixekizumab during the pregnancy.

The analysis also included 76 men (1.7%) who were exposed to ixekizumab and who fathered a child. Of these pregnancies, 64 had a known outcome. They resulted in 51 live births (79.7%); 44 of them (86.3%) were full term, and 5 (9.8%) premature. There were 10 spontaneous (15.6%) and 3 induced abortions (4.7%). Five (7.8%) congenital malformations were reported for paternal exposure (i.e. heart abnormality, triplets, low birth weight, abnormal growth according to ultrasound, webbed fingers, and widening of right pelvis). In the PSOLAR registry, 93% of live births were full term, and 90% in US birth records [2]. Reporting rates of spontaneous and induced abortions in PSOLAR were 21.7% and 7.2%, respectively.

Although data on pregnancies in patients with psoriasis or psoriatic arthritis exposed to ixekizumab in clinical studies are limited due to the small number of events and the short exposure/observation periods, they complement the available information. Reported pregnancy outcomes in patients exposed to ixekizumab were comparable with reports from female patients in PSOLAR and in the US birth records. "Despite the limitations, this data is quite comforting to look at," concluded Prof. Egeberg.

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New Insights in Photoprotection

Systemic photoprotection: a valuable addition to topical sun protection

Systemic sun protection is an interesting additional way to shield the at-risk group. A fern extract has shown promising results for this indication due to its strong antioxidant properties [1].

"Oral photoprotective agents do not substitute but complement conventional photoprotection," said Prof. Salvador González Rodriguez (University of Alcala de Henares, Spain). An additional protection, in particular for high-risk groups, is necessary due to the limitations of topical sunscreens: they are re-applied to infrequently, the quantity of the applied product is usually too small, and they are subject to unnoticed removal by perspiration [2,3]. Although wearing protective clothing and applying a broad-spectrum, water-resistant sunscreen with a sun protection factor of at least 30 are still the most reliable methods of sun protection, this might not be sufficient for high-risk groups. "The problem with topical sunscreen is that there is no universal application; therefore, we also need a systemic protection," said Prof. González Rodriguez.

The most promising results regarding oral sun protection come from an extract of a Central American fern plant, Polypodium leucotomos. Studies have shown photoprotective, immune-modulatory, and antioxidative properties of the fern extract [4]. Polypodium leucotomos is a powerful antioxidant due to its high content of phenolic compounds [5]. It not only inhibits the generation of reactive oxygen species (ROS) by ultraviolet (UV) light but also prevents UV-induced and ROS-induced DNA damage.

A study in healthy patients showed that the fern extract is an effective chemophotoprotector against PUVA-induced skin phototoxicity: skin treated with the fern extract revealed a significant numeric reduction of sunburn cells, preservation of Langerhans' cells, decrease of tryptase-positive mast cell infiltration, and decrease of vasodilation [6]. The extract also inhibits mitochondrial DNA damage induced by UVA, and matrix metalloproteinases (MMP)-1 expression induced by visible light and infrared radiation.

In addition, it blocks the photoisomerisation and photo-decomposition of trans-urocanic acid to cis-urocanic acid, which partially affects Langerhans cells and mast cell degranulation, thereby contributing to UV-induced immunosuppression [7]. These cellular and molecular effects are reflected in inhibitions of carcinogenesis and photoaging.

In addition to its antioxidant activity, the fern extract bears promise in the treatment and prevention of photoaging due to its proven effects on extracellular matrix remodelling. The fern extract inhibits several MMPs by inducing elastin and different types of collagen; thus, promoting regeneration of the skin [8].

"I think that systemic photoprotection is of particular relevance in high-risk patients like lighter skin phototypes, patients with photodermatosis and photoaggravated dermatosis, pigmentation disorders patients, patients with a clinical history of skin cancer, and patients under phototherapy, as adjuvant treatment," concluded Prof. González Rodriguez.

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The underestimated effect of visible light

Until recently, visible light (400-700 nm) has been regarded to have no significant cutaneous photobiologic effects [1]. However, they contribute to the ROS production and to skin damage attributed to UV light.

"We should not forget that not only UV light but also visible light contributes to the production of ROS," said Dr Serena Lembo (University of Naples Federico II, Italy). Irradiation of human skin equivalents with visible light has been shown to induce production of ROS, proinflammatory cytokines, and matrix metalloproteinases (MMP)-1 expression in a dose dependent manner [2]. Another trial assessed the free radical induction by sunlight in different spectral regions [3]. It showed that although UV light stimulated the most intensive radical formation, visible light and even near infrared light also considerably contributed to the free radical formation. Half of all free radicals generated in the whole solar spectrum are induced by visible light and near infrared light [3]. According to this trial, visible light energy is not potent enough to produce radicals directly. However, within the mitochondria and by the activity of several enzymes, ROS are produced. The effect of visible light in the extracellular matrix is very similar to UV radiation: it increases MMP-1 and MMP-9 expression and decreases type 1 procollagen levels in human skin in vivo, thus contributing to photoaging [5].

Visible light penetrates deep into the dermis. The erythema is considered a result of dilatation of the vasculature of the subpapillary plexus. Production of radicals also induces inflammatory processes and this chronic process might contribute to DNA damage and carcinogenesis. Although sunscreens effectively protect against UV radiation, they are not as efficient stopping visible light and infrared light. Thus, the levels of skin ROS may still overcome the natural antioxidant reservoir in the skin and cause skin damage [2,4].

Dr Lembo also mentioned a study that showed that immediate pigment darkening induced by visible light is not significantly different from that produced by UV [6]. "In this study, visible light even induced a more potent and more long-lasting pigmentation compared with UVA1," said Dr Lembo. Compared with UVB irradiation, the shorter wavelengths of visible light, the blue-violet light, induced a significantly more pronounced hyperpigmentation that lasted up to 3 months, but only in melano-competent individuals [7]. These finding have potential implications due to the possible role of visible light in the pathogenesis of pigmentary disorders, such as melasma.

In another study, commercially available sunscreens were found to have minimal effects on reducing visible light-induced ROS. Results showed that MMP-1 expression following infrared radiation can be prevented by the addition of appropriate antioxidants [8]. Thus, increasing the antioxidant threshold of the skin is a method to increase the buffering ability of the skin against ROS induced by visible light. A poster presented during the EADV 2019 meeting demonstrated that addition of the antioxidant resveratrol can also be used successfully as a photostabiliser of a chemical UVA filter in sunscreen products, thus killing two birds with one stone [9].

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Urticaria

Comorbidities more common in chronic urticaria, psoriasis, and AD

A German study identified several comorbid diseases that have a high prevalence in patients with chronic urticaria, psoriasis, and atopic dermatitis (AD); thus, adding to their burden of disease [1].

Data for this study was obtained from a representative subset of anonymised German health insurance claims containing information of about 4 million insured people [1]. Included were 2,561 adults and 216 paediatric patients with chronic spontaneous urticaria (CSU). For psoriasis, 72,738 adults were included and 747 paediatric patients, as well as 61,030 adults with AD and 30,180 children. The study also contained a reference group of 3,243,744 adults and 576,234 children/adolescents matched according to age and sex to investigate for comorbidity prevalence. Of the adults, 50% were male, and 51.4% of the children were male. Mean age of adult and paediatric patients was 52.2 years and 10.6 years for CSU. Respective values for psoriasis were 59.1 and 12.5, for AD 47.7 and 7.72. All patients had to be observable throughout the entire year of 2017. They were included based on their specific ICD-10 code for diagnosis.

Over all 3 diseases the researchers found correspondingly increased frequencies for anxiety and depression in adult patients when compared with the matched subjects. The paediatric patients were more prone to these diagnoses than the controls, but not as much as the grown-ups. Looking especially at results for CSU, Dr Karsten Weller (Charité University Hospital, Germany) and his fellow researchers found augmented values for prevalence of comorbidity for allergic rhinitis (24.8%), arthropathies (44.5%), dermatitis and eczema (38.4%), and hypertension (41.7%) in adults with CSU. Rates for adults with psoriasis and AD were similar with the exception of autoimmune thyreoiditis, which was clearly more frequent in CSU.

In children with CSU, concurrent diagnoses of asthma (15.6%) and allergic rhinitis (25.6%) stood out. The corresponding rates in the control group were 6.03% and 5.53%, respectively. This large data analysis confirms a high prevalence of physical and psychiatric comorbidities in adult and paediatric CSU patients. The authors emphasised that due to their very specific inclusion criteria for CSU patients in this study, they probably underestimated the prevalence of CSU in Germany.

1. Weller K, et al. P0930, EADV 2019, 9-13 Oct, Madrid, Spain.

D-Dimer as future biomarker in CSU management?

An Italian study investigated coagulation cascade activation in the context of chronic spontaneous urticaria [CSU]. The identified D-Dimer values were correlated to disease activity.

The exact pathogenesis of mast cell activation in CSU is still not entirely clear [1]. Recent findings imply a role not only of the immune system dysregulation and activation of the inflammatory cascade, but also of the coagulation pathway in CSU pathogenesis. Dr Antonio Cristaudo (San Gallicano Dermatological Institute, Italy) and his colleagues looked into the involvement of coagulation factors [2]. They were particularly interested in a possible capacity of D-dimers and/or prothrombin fragments F1+2 to anticipate treatment response to omalizumab in CSU patients. 40 patients were included into the trial. Prerequisite for enrolment was the presence of wheals with or without presence of angioedema for ≥ 6 weeks. Laboratory testing was performed for activation markers of complement C3 and C4, prothrombin and partial thromboplastin time together with markers of coagulation activation and D-dimers in the plasma.

The assessment revealed a direct correlation of the amount of D-dimer with severity of CSU. Of ther participants, 20% were being treated with omalizumab due to their inadequate disease control with antihistamines. In a preliminary analysis, the investigators found a reduction in D-dimer plasma values in those who had good response to omalizumab therapy. They estimate that D-dimers may qualify as predictor of clinical response to omalizumab treatment and as a biomarker for CSU severity.

1. Puxeddu I, et al. J Asthma Allergy. 2019;12:285-295.
2. Cristaudo A, et al. P1978, EADV 2019, 9-13 Oct, Madrid, Spain.

Ligelizumab for CSU: symptom control and high response rates in re-treatment

Depending on the dosing, ligelizumab has displayed more symptom control in chronic spontaneous urticaria [CSU] than omalizumab. In case of re-occurrence of active CSU after stop of therapy, response rates with ligelizumab re-treatment were very encouraging.

Chronic urticaria is a common, mast cell-driven disease with an increasing world-wide incidence [1]. Ligelizumab, a monoclonal anti-IgE antibody that prevents the cascade of allergic reaction by inhibiting the binding of free IgE to mast cells and basophils has higher affinity to IgE than omalizumab [2,3]. A recently published core 2b randomised controlled trial with 382 adult CSU patients, compared response rates of CSU to ligelizumab at different doses to omalizumab and placebo [1].

One of the questions that Dr Marcus Maurer and colleagues set out to answer was how long after a withdrawal of ligelizumab the patients with complete response would experience a loss of efficacy [4]. Attaining complete response was defined as UAS7=0 at week 20. Patients (n=382) were randomised to omalizumab (300 mg), ligelizumab (24 mg, 72 mg, 240 mg), or placebo. Post-treatment monitoring lasted for up to 24 weeks.

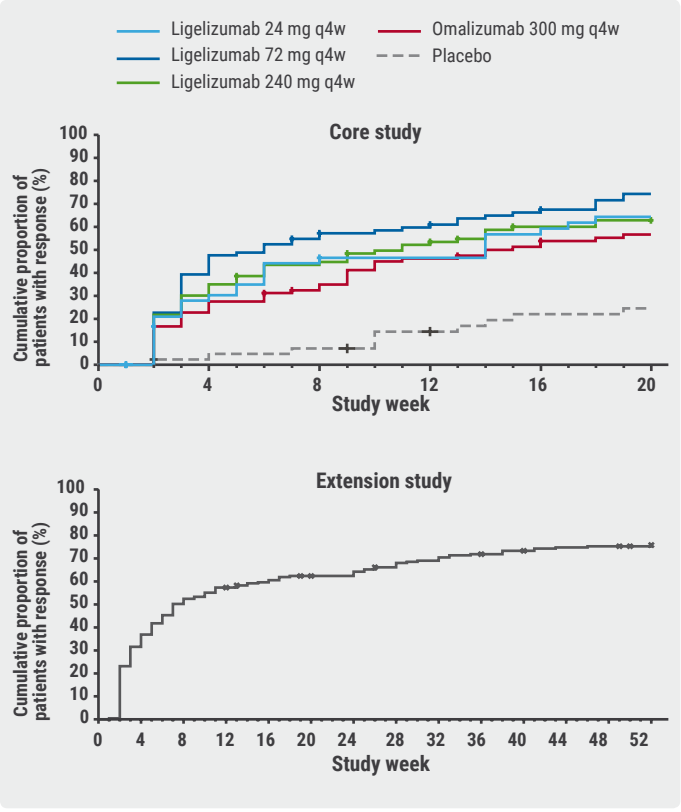
Results found that ligelizumab demonstrated a clear dose-response relationship. At doses of 72 mg or 240 mg, the drug induced a fast and sustained symptom control in a greater rate of patients than omalizumab or placebo. Depending on the allocated dosage of ligelizumab, it took a median of 3 (24 mg), 4 (72 mg), or 10.5 (240 mg) weeks until loss of complete response. The median period for omalizumab was 4 weeks and for placebo 1 week.

Results with focus on complete hives response were concurrent. The respective median time observed was 3, 4, and 9.5 weeks for ligelizumab treated patients compared with 4 weeks for omalizumab. Thus, ligelizumab 240 mg showed longer symptom control maintenance than omalizumab 300 mg.

Good efficacy in case of re-treatment

To further investigate the potential of ligelizumab, an open label, single-arm extension of the core trial was conducted [3]. Included patients had signs of active CSU after a wash out phase of 16 weeks. The following treatment phase with 240 mg ligelizumab lasted for 52 weeks; follow-up was done until week 104. At week 4, the re-treatment resulted in a complete resolution of symptoms in a week according to the Urticaria Activity Score (UAS) 7=0 of 36.9% of patients at week 4, 62.4% at week 20, and 75.8% at week 52 (see Figure). The respective cumulative response rates of well-controlled symptoms with UAS ≤ 6 were 58.7%, 76.8%, and 84.2%, respectively.

Figure: Kaplan-Meier plot of weeks until achievement of UAS7=0 in the 2 b core study and the 1-year extension trial [3]



In summary, patients experiencing relapse after the end of treatment had similar or yet higher response rates in the extension phase than under the preliminary treatment in the core study. Two phase 3 trials investigating efficacy and safety of ligelizumab 72 mg and 120 mg every 4 weeks for CSU patients are ongoing.

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2. Hu J, et al. Clin Transl Allergy.2018;8:27.
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Rosacea – From New Spectrum to New Therapy

The Rosacea Tracker may aid clinical decision-making

The ROSCO panel developed a tracking tool to help clinicians continuously follow the disease developments of their rosacea patients that comprises clinical as well as quality-of life-features. This may contribute to facilitating the best possible individualised care.

In the wake of the change to a phenotype-based approach to rosacea, the Rosacea Consensus (ROSCO) group saw the need to develop a comprehensive longitudinal monitoring tool [1]. Taking care of patients suffering from this chronic disease involves long-term management with modifications in therapy whenever clinical features change. The new Rosacea Tracker is supposed to offer an option to document changes in rosacea disease features for physicians, as well as an option to record patient-reported clinical changes and influence on patients' quality of life. Collecting this evidence could enable the physician to decide if and when altering the management is indicated.

The global 2019 ROSCO group comprises 19 dermatologists and 2 ophthalmologists. They used a modified Delphi method to answer various questions as a base for the Rosacea Tracker prototype. The participants received these questions via a blinded e-survey. Per definition, a consensus was reached if ≥75% of the participants responded to a question with 'agree' or 'strongly agree'. As a result, the Rosacea Tracker consists of distinct sheets to be completed by the physician and by the patient. In addition, instructions on how to report on disease features were documented in separate user guides. The instructions and their presentation were rated 'clear" by most of the panel members (18/21 and 17/21).

Physicians should assess severity of features in different grades: cutaneous with grade 0 (clear/none) to 4 (severe), ocular with grade 0 (clear/none) to 4 (severe: sclerokeratitis/ anterior uveitis). The answers to questions on the impact of rosacea on the patient's quality of life were also categorised in 4 steps: from 0 (not at all) to 4 (very much). Among the 10 cutaneous signs included in the physician's sheet were: transient/persistent centrofacial edema, (non-)inflamed phyma, burning sensation, telangiectasia, and papules/ pustules. The ocular sheet features 8 findings, including blepharitis, conjunctivitis or dry/gritty/ foreign body sensation.

The authors anticipate the Rosacea Tracker to become a very helpful tool for clinical practice. As further validation and refinement is endorsed, a number of panel members will now introduce the Rosacea Tracker in their clinics.

1. Tan J, et al. P0024, EADV 2019, 9-13 Oct, Madrid, Spain.

New guidance on rosacea therapy according to phenotype

A practical algorithm for choosing the right treatment option has been developed by the ROSCO group for the 7 most common phenotypes of rosacea, as current management in clinical practice should be based on the features of the disease [1].

In his talk, Prof. Bernard Cribier (Strasbourg University Hospital, France) noted that the classification of rosacea according to stages is obsolete as there is considerable overlap of rosacea features between the traditionally used stages and subtypes. This is in line with the global 2019 ROSCO group's update of their feature-based approach for classification and management decisions [2-4]. "With the new ROSCO approach, you just describe what you see and it is easier to pick a therapy according to the phenotype," Prof. Cribier said.

Based on contemporary publications, the new treatment ROSCO recommendations revise the 2017 guidance particularly with regard to 3 points: (1) although there is insufficient evidence supporting the use of oral beta-blocker or topical alpha-adrenergic modulating drugs for flushing, they could be considered due to clinical experience; (2) for persistent centrofacial erythema, vascular lasers constitute a supplementary choice of therapy; and (3) due to the risk of depigmentation, application of vascular lasers like pulsed-dye lasers (PDL) and intense pulsed light (IPL) on darker skin should be considered by an experienced healthcare provider [5].

Table: 2019 ROSCO guidance for treatment of rosacea by a feature-driven approach [5]

	FIRST-LINE TREATMENT OPTIONS	FEATURE																	
		Transient erythema (flushing)			Persistent erythema			Inflammatory papules/pustules			Telangiectasia			Phyma (clinically inflamed)			Phyma (clinically non-inflamed)		
		MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
TOPICAL AGENTS	GENERAL SKINCARE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	α-ADRENERGICS	●	●	●	●	●	●												
	AZELAIC ACID							●	●										
	IVERMECTIN							●	●	●									
	METRONIDAZOLE							●	●										
ORAL AGENTS	ß-BLOCKERS	●	●	●															
	DOXYCYCLINE							●	●	●				●	●	●			
	ISOTRETINOIN									●				●	●	●			
PROCEDURES	ELECTRODESICCATION										●	●	●						
	INTENSE PULSED LIGHT				●	●	●				●	●	●						
	VASCULAR LASER				●	●	●				●	●	●						
	PHYSICAL MODALITIES																●	●	●

Prof. Martin Schaller (University of Tübingen, Germany) and his colleagues presented their practical algorithm for the treatment of rosacea according to 7 common phenotypes [5]. They consisted of:

A) the clinically inflamed phyma with persistent centrofacial erythema,
B) the clinically inflamed phyma with papules and pustules plus persistent centrofacial erythema,
C) persistent centrofacial erythema with papules and pustules,
D) the clinically inflamed phyma,
E) the clinically inflamed phyma with papules and pustules,
F) the clinically non-inflamed phyma, and
G) the persistent centrofacial erythema.

For all phenotypes, sunprotection and general skincare belong to the general advice to the patient (see Table). Apart from the clinically inflamed and non-inflamed phyma, all patients should also be encouraged to avoid triggers for rosacea.

For patients suffering from rosacea of the A, B, D, or E phenotype, anti-inflammatory topical and/or oral treatments combined with or followed by physical modalities are recommended. For patients with features of type C, there are 2 parallel suggestions of treatment: either the use of topical alpha-adrenergic modulation agents and/or IPL or vascular laser or therapy with anti-inflammatory topicals and/or oral treatments. For rosacea in form of persistent centrofacial erythema, topical alpha-adrenergic modulation agents and/or IPL or vascular laser are endorsed. Whenever centrofacial erythema is present in a patient, IPL or vascular laser could be considered preceding topical use of alpha-adrenergic drugs. The use of oral antibiotics combined with topical agents may be justified in patients with extensive papules and pustules.

1. Cribier B. PLB01, EADV 2019, 9-13 Oct, Madrid, Spain.
2. Scaller M, et al. Br J Dermatol. 2019 Aug 7. [Epub ahead of print]
3. Gallo RL, et al. J Am Acad Dermatol. 2018;78:148-155.
4. Van Zuuren EJ, et al. Br J Dermatol. 2019;181:65-79.
5. Schaller M, et al. P0028, EADV 2019, 9-13 Oct, Madrid, Spain.

Best of the Posters

Above-the-neck melanoma more prone to metastases

Dividing melanomas according to their location above or below the neck, British researchers found a higher likelihood of above the neck tumours to spread.

Numbers for newly diagnosed malignant melanoma are mounting, with the highest prevalence in Caucasians [1]. In males, this type of cancer has currently the fastest increasing incidence rate in the United Kingdom. Worldwide, malignant melanoma is most common in New Zealand and Australia.

"In this study, we have reviewed new malignant melanoma diagnoses to see which ones are more likely to metastasise in terms of location," said lead investigator Dr Mohammed Al Abadie (Cross Hospital; Cannock Chase Hospital, United Kingdom). A total of 45 patients were included into the study. The diagnosis of malignant melanoma had been established through biopsies. According to tumour location, 37 patients were assigned to a group with melanomas below the neck while 8 had above neck malignant melanomas. CT-scans were used for staging, and sentinel lymph node biopsies were offered to all patients with stages 2 or higher. In the group of below neck tumours, no distant metastases were identified and only 1 patient (2.7%) had a positive biopsy of the sentinel lymph node. Lymph node melanoma was found in both patients that agreed to sentinel lymph node biopsy in the above neck group. These 2 patients also had distant metastases.

1. Al Abadie, et al. P0672, EADV 2019, 9-13 Oct, Madrid, Spain.

Reduced sleep quality in dermatoses influenced by itch and pain

Patients with hidradenitis suppurativa (HS), atopic dermatitis (AD), and plaque psoriasis often experience sleeping problems. In HS, pain and itch increases the frequency of insomnia, and the pain was associated to poor sleeping quality [1].

Dermatoses like HS, AD, and psoriasis entail varying intensities of itch and pain that can have a negative influence on the quality of life of the affected patients. Dr Karolina Kaaz (Wroclaw Medical University, Poland) and her colleagues evaluated the influence of itch and pain on the sleep of HS patients and compared this with AD and psoriasis patients. Data on 108 patients with HS, 100 with AD, and 100 with psoriasis were included. The HS patients had a mean age 36.3, 47% was female, and their mean Hidradenitis Severity Score was 34.8. In the AD group, 42% was female, mean age 39.2, and patients had a mean Scoring of Atopic Dermatitis (SCORAD) of 33.6, while the psoriasis patients were aged 44.1 years, 39% was female, and they had a mean Psoriasis Area and Severity Index score (PASI) of 13.5.

Itch and pain were assessed using a visual analogue scale (VAS). Insomnia and sleep quality were evaluated by the Athens Insomnia Scale (AIS) and the Pittsburgh Sleep Quality Index. The 3 groups showed mean values in Dermatology Life Quality Index (DLQI) of 13.0 (HS), 16.4 (AD), and 12.8 (psoriasis). Severe itch was only present in 14% of HS, but 60% of AD and 46% of psoriasis patients. Looking at pain rates in the HS group, the investigators found 21% severe, 17% moderate, and 42% mild pain. 66% of the AD and 83% of the psoriasis subjects did not report any pain and only 13% of AD and 11% of psoriasis patients suffered from severe pain.

In HS patients, a significant correlation between grade of itch/pain and AIS scores was found (P=0.03). Mean AIS scores for HS were lower than those in AD (P<0.0001) and psoriasis (P=0.02). With mean total scores of 6.5, 8.3, and 8.1, 70% of HS and 80% of AD/PP patients were over the cut-off value of ≥ 5, which stands for poor sleeping quality. In HS, the magnitude of itch and pain correlated to the established AIS values.

The authors concluded that the impact of itch was important for patients of all 3 chronic dermatoses. Especially for HS, they emphasised that itch and pain did not only affect insomnia incidence, but pain also influenced sleep quality.

1. Kaaz K, et al. P1846, EADV 2019, 9-13 Oct, Madrid, Spain.

Anxiety and depression are common in families of AD infants

Three out of four family members and caregivers of young children with atopic dermatitis (AD) suffer from mild anxiety and depression. This was shown in a study conducted at the University Clinic in Skopje (Macedonia) [1].

Anxiety and depression is often overlooked and underdiagnosed both in patients, as well as in family members and caregivers of pre-school children. AD is a considerable burden, also for family members. In addition, the clinical spectrum of AD often includes insomnia, which can also affect the parents of small kids.

To evaluate the psychosocial effect of AD on their family members and caregivers, researchers from the Phi University Clinic of Dermatology in Skopje sent out a 7-item questionnaire in which they asked about the greatest worries of caregivers. It also contained a Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating scale (HAM-A) for evaluation of the symptoms of depression and anxiety of family members and caregivers of 35 patients with AD aged 1 to 6. The severity of AD was scored using the Scoring of Atopic Dermatitis (SCORAD).

A total of 83 family members and caregivers were evaluated. All questionnaire respondents reported at least mild-severity anxiety with some showing moderate-severity anxiety. The average score on the HAM-A scale was 12.9 ± 4.8. In

addition, almost 3 in 4 (74%) participants were also found to suffer from depression. Interestingly, the highest HAM-A and HAM-D score were not associated with the highest SCORAD values, but with persistence and longevity of AD. The most frequent worry reported by the families was the information families and caregivers received about the nature of the disease itself, since AD is a long-term condition which requires complex and costly medical treatments.

Dr Vesna Grivcheva-Panovska said: "The chronicity and complexity of chronic dermatitis often leads to overlooked anxiety and depression in family members and caregivers and our results show that the extent of this cannot be overstated. In the future, we must take a wholesome view of the situation and a widened approach to the management of AD, not only for the patients but for their families as well." Keeping this in mind, dermatologists should actively look for symptoms of depression or anxiety in families with AD, and, if necessary, refer affected persons to specialists.

1. Grivcheva-Panovska V, et al. P0273, EADV 2019, 9-13 Oct, Madrid, Spain.

Certolizumab pegol efficacious for head and neck psoriasis

A pooled analysis of the phase 3 CIMPASI-1 and CIMPASI-2 studies with focus on psoriasis of head and neck showed that certolizumab pegol, an anti-TNFα monoclonal antibody, in a dose of 400 mg every second week leads to greatest improvement of this difficult-to-treat area [1].

The new assessment included data from 461 adult patients with moderate-to-severe psoriasis from the CIMPASI-1 and CIMPASI-2 trials. The analysis focussed on the head and neck was chosen, as visible psoriasis in these areas has a disproportionately high impact on patients' quality of life [2]. Inclusion criteria also included a Psoriasis Area and Severity Index score (PASI) of ≥ 12, body surface area (BSA) ≥ 10%, and Physician's Global Assessment (PGA) of ≥ 3 at baseline. Randomisation allocated 186 patients to the group treated with 200 mg certolizumab pegol every second week, 175 patients receiving 400 mg certolizumab every second week, and 100 patients to placebo. The initial treatment within the RCTs lasted over 16 weeks. All study participants reaching at least a 50% improvement of PASI (primary study endpoint) continued maintenance at the previous dosage through week 48. Co-primary endpoints were: PASI75 defined as responder rate along with PGA of 0/1 and improvement of ≥ 2 points.

The post-hoc analysis analysed achievement of 75% and 90% improvement of psoriatic lesions on head and neck and the mean difference from baseline in these locations. Mean score values for PASI on head and neck before treatment were 2.1 in the lower certolizumab dose group, 2.4 in the higher dose group, and 2.4 in the placebo group.
At week 16, 80% of the patients taking the higher dose of certolizumab and 70.4 % of those in the 200 mg certolizumab group reached PASI 75 on head and neck, compared with 14.9% of the patients on placebo (see Figure). Rates for PASI 90 were 70.3%, 56.8%, and 9.3%, respectively. Response was lasting through week 48 with changes from baseline of -88.3% with the 400 mg dose and -76.5% with the 200 mg dose. All in all, these results indicate that certolizumab is an effective treatment for head and neck psoriasis.

1. Van de Kerkhof P et al. P1617, EADV 2019, 9-13 Oct, Madrid, Spain.
2. Merola JF, et al. Dermatol Ther. 2018;31:e12589.

Figure: Improvements in PASI of the head and neck region through weeks 0-48 [1]